REMARKS / ARGUMENTS

The Final Office Action mailed November 30, 2005, has been received and reviewed. Claims 1-23, 26, 28-59, and 61-68 are currently pending in the application. Claims 24, 25, 27 and 60 have been cancelled. Claims 28-43 and 51-59 are withdrawn from consideration as being directed to a non-elected invention. Hence, claims 1-23, 26, 44-50 and 61-68 are under consideration, and are rejected. While not explicitly stated in the Final Office Action, it is believed that amended claims provided in the Supplemental Amendment (filed September 8, 2005) were entered into the record.

Applicants are filing this response under 37 C.F.R. § 1.116 in order to request reconsideration of the entered claims in view of the recent, relevant, decision by the United States Court of Appeals for the Federal Circuit (Federal Circuit) in Invitrogen Corporation v. Clontech Laboratories, Inc. (429 F.3d 1052) (Fed. Cir. 2005), a copy of which is being included with this response as *Exhibit A*. The rejections maintained in the Final Office Action (mailed November 30, 2005) will be discussed in the context of the Federal Circuit's ruling in this case.

Applicants respectfully request that this response, and these remarks and arguments, be entered into the record, in preparation for an anticipated appeal from the final rejections by the Examiner in the instant case.

Claim Amendment

Only claim 28 has been amended, as shown above, to make it dependent upon claim 1, instead of claim 8; thereby better differentiating it from withdrawn claim 37. Entry of this amendment is respectfully requested, since it places the claims in better condition for rejoinder, should claims 1 and 8 be found to be allowable. Applicants hereby submit that this amendment should be entered into the record since it adds no new matter to the Application, requires no additional search, and places the claims in better condition for allowance or appeal.

Invitrogen Corporation v. Clontech Laboratories, Inc.

(429 F.3d 1052) (Fed. Cir. 2005).

The issue of written description and enablement of biotechnological inventions under 35 USC § 112, first paragraph, was recently considered by the Federal Circuit in Invitrogen. *See Exhibit A.* At issue in Invitrogen were three patents-in-suit that each disclose and claim a genetically modified reverse transcriptase (RT) in terms of two distinct functional attributes – namely an RNA-dependent DNA polymerase ("reverse transcriptase" or RT) activity, and an RNA-DNA hybrid-specific nuclease (RNase H) activity. The disputed claims made use of these functional attributes to define the invention. Importantly, the claims allowed in these patents are of considerable breadth, since they encompass isolated polypeptides encoded by a "modified reverse transcriptase nucleotide sequence," wherein said nucleotide sequence is derived from a variety of organisms. Claim 1 of U.S. Patent No. 6,063,608 (the '608 patent) is representative. It reads:

> 1. An isolated polypeptide having DNA polymerase activity and substantially reduced RNase H activity, wherein said polypeptide is encoded by a modified reverse transcriptase nucleotide sequence that encodes a modified amino acid sequence resulting in said polypeptide having substantially reduced RNase H activity, and wherein said nucleotide sequence is derived from an organism selected from the group consisting of a retrovirus, yeast, Neurospora, Drosophila, primates and rodents.

'608 patent, col. 19, lines 26-34 (claim 1), which has been provided with this response as *Exhibit B.*

As noted by the Federal Circuit, "[w]ith these patents Invitrogen thereby claims a compound (the polypeptide or genetically engineered RT) in terms of biological function (DNA polymerase and RNase H activity)." *Id.* at 1072.

In Invitrogen, which was an appeal from the judgement of the United States District Court for the District of Maryland, the validity of the claims of '608 patent, and other patents-in-suit, was called into question under 35 USC § 112, first paragraph's, written description and enablement requirement by the defendant, Clontech Laboratories, Inc. Ultimately, the validity of the claims and the descriptions upon which they are based

– particularly as relates to 35 USC § 112, first paragraph written description and enablement – were upheld.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph in the Instant Case

Claims 1-23, 26, 44-50 and 61-68 of the instant Application are finally rejected under 35 U.S.C. § 112, first paragraph, as being based upon a disclosure that allegedly provides insufficient enablement AND written description. The claims allegedly contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Further, the claim(s) allegedly read upon subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully disagree with these allegations, and assert that the as-filed specification provides sufficient written description and enablement of the claimed invention under the standards promulgated by the Federal Circuit in Invitrogen Corporation v. Clontech Laboratories, Inc. (429 F.3d 1052) (Fed. Cir. 2005).

Written Description

Applicants note that unlike conception and enablement, compliance with the written description requirement is a question of fact, and invalidating a claim under 35 USC § 112, first paragraph requires a showing by clear and convincing evidence that the written description requirement has not been satisfied. Enzo Biochem, Inc. v. Gen-Probe, Inc., 323 F.3d 956, at 962-63 (Fed. Cir. 2002). Applicants respectfully assert that in the present case, the Examiner has failed to provide a showing by clear and convincing **evidence** that the written description requirement has not been satisfied. Instead, the Examiner's arguments comprise only allegations, which are not supported by any cited evidence, and in some cases (e.g., "[t]he claims do not require that the binding domain be present or intact....," Final Office Action, page 3, line 15), are simply not consistent with the facts.

The United States Patent and Trademark Office (PTO) issued guidelines for the examination of patent applications under the 35 USC § 112, first paragraph, written description requirement. These guidelines state that the written description requirement of 35 USC § 112, first paragraph, can be met by

> show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

Guidelines for Examination of Patent Applications under 35 USC § 112, first paragraph, "Written Description" Requirement, 66 Fed. Reg. 1099, 1106 (Jan. 5, 2001) (emphasis added).

These standards were first adopted by the Federal Circuit in Enzo at 964. In University of Rochester v. G.D. Searle, 358 F.3d 916 (Fed. Cir. 2004), the Federal Circuit reiterated its approval of Enzo's use of the PTO's written description guidelines, and very recently, the Federal Circuit reaffirmed and applied these standards in Invitrogen Corporation v. Clonetech Laboratories, Inc., 429 F.3d 1052 (Fed. Cir. 2005).

As noted above, in Invitrogen, which was an appeal from the judgement of the United States District Court for the District of Maryland, the validity of the claims of Invitrogen's '608 patent, and other patents-in-suit, was called into question under 35 USC § 112, first paragraph's, written description requirement by the defendant, Clontech Laboratories, Inc. Clontech argued that University of California v. Eli Lilly & Co., 119 F.3d 1559 (Fed. Cir. 1997) compels the conclusion that the claims-in-suit fail the written description requirement because they "do not recite the DNA or protein sequences as required" by Eli Lilly, at 1566-69, and Fiers v. Revel, 984 F.2d 1164, 1171 (Fed. Cir. 1993). Further, according to Clontech, the district court erred in finding sufficient structure in the DNA sequence recited in the common specification, and within the knowledge of one of ordinary skill in the art, **because the claims at issue "are not limited to sequences recited in the specification** and do not recite DNA or protein sequence." Invitrogen 429 F.3d at 1073 (emphasis added).

Close examination of the '608 patent specification (See *Exhibit B*) reveals that while it discloses two different nucleotide sequences (one in Figure 6 and from columns 5 through 8, and one from columns 2 through 6) that potentially encode two different embodiments of the claimed invention, both of these nucleotide sequences are derived from a single source – the Maloney-Murined Leukemia Virus (M-MLV; a retrovirus) – and only the first of these (the RT coding sequence of plasmid pRTdEcoRV-C that encodes the N-terminal-most 504 amino acid residues of M-MLV RT) was shown to encode a polypeptide having the functional features of the claimed invention. In other words, in total, the '608 patent specification provided only ONE specifically described working embodiment of the invention that had actually been reduced to practice.

In response to Clontech's arguments regarding the written description requirement, the Federal Circuit ruled:

> "Clontech's appeal to Eli Lilly and Fiers is misplaced. In those cases, the patent specifications at issue did not identify the sequence (structure) of **any** embodiment of DNA claimed therein. ... In contrast, the shared written description for the patents-in-issue recites both the DNA and amino acid sequences of **a** representative embodiment of the claimed RT enzyme. The specification also discloses test data that **the** enzyme produced by **the** listed sequence **has the claimed features** – DNA polymerase activity without RNase activity. Under both the Eli Lilly and Fiers analysis, the specification at bar is sufficient.
>
> In short, ... the claims in the patents-in-suit satisfy the written description requirement of § 112."

Invitrogen, at 1073-4 (emphasis added).

In view of this ruling, it is clear that the written description requirement for a claim that reads upon "a modified reverse transcriptase nucleotide sequence that encodes a modified amino acid sequence resulting in said polypeptide having substantially reduced RNase H activity, and wherein said nucleotide sequence is derived from an organism selected from the group consisting of a retrovirus, yeast, Neurospora, Drosophila, primates and rodents" had been met, in the eyes of the Federal Circuit, by the disclosure of a **single representative embodiment** of the claimed RT enzyme that had been shown to have the claimed functional features. Further, according to the Federal Circuit, under both the Eli Lilly and Fiers analysis, the specification at bar was sufficient

– even though it only disclosed a single functional representative embodiment of the claimed invention described in the considerably broad claims.

In the present case, the Examiner states in the Final Office Action (page 3, lines 17 & 18) that: "The written description is shown by disclosing **enough examples commensurate with the claims**." Applicants respectfully point out that the raised bar of the examiner's interpretation of the law is clearly at odds with the cogent decision of the Federal Circuit, who, in Invitrogen, concluded that a **single representative embodiment** of the claimed RT enzyme, having the claimed functional features, was sufficient to satisfy the written description requirement of § 112 for a remarkably broad claim.

Furthermore, in the present case, the pending claims are drawn to isolated protein complexes "having a first protein interacting with a second protein," or "wherein said first and second proteins interact to form said isolated protein complex." Despite the inclusion of this functional limitation into the claims, and despite the disclosure in the specification that "the UEV domain of the Tsg101 protein and the PTAP motif [of the late domain] of the HIV GAGp6 are responsible for the interactions" (Specification, page 38, lines 5-6) the Examiner has alleged "the claims do not require that the binding domain be present or intact." When viewed relative to the fact pattern considered by the Federal Circuit in Invitrogen, this conclusion by the Examiner would be equivalent to the Federal Circuit saying "claim 1 of the '608 patent does not require that the DNA polymerase catalytic domain be present or intact," despite the fact that claim 1 of the '608 patent reads upon "[a]n isolated polypeptide having DNA polymerase activity and substantially reduced RNase H activity."

Applicants respectfully assert that, as would be immediately recognized by one of ordinary skill in the art, the binding domains responsible for the interaction between Tsg101 and HIV GAGp6 – or their equivalents – must be present and intact in order for the first and second proteins of the pending claims to interact and form the claimed isolated complex – as required by the claims. In other words, the pending claims clearly include the limitation that the first protein must interact with the second protein, and the specification clearly indicates that the UEV domain of the Tsg101 protein and the PTAP motif of the late domain of the HIV GAGp6 are responsible for the interactions. Therefore, contrary to the allegation of the Examiner, the pending claims – in their

current form – DO require that the binding domains be present or intact, by virtue of the functional limitation that the claimed protein complex is formed by the interaction of the first protein with the second protein.

With respect to the Examiner's assertion that "[t]he written description is shown by disclosing enough examples commensurate with the claims," and the Federal Circuit's considerably lower bar, as revealed in Invitrogen, Applicants respectfully note that the instant specification certainly goes well beyond the requirement of a single representative embodiment required by the Federal Circuit in Invitrogen. For example, Table 1 on page 14 provides one representative embodiment of the present invention that was reduced to practice. Table 1 indicates that a 52 amino acid fragment of HIV Gag (comprising the GAGp6 late domain) interacts with amino acid residues 7 through 390 of Tsg101. Additionally, Example 3 (pages 81-83) shows that a first fusion protein comprising full-length Tsg101 fused to a transcriptional activation domain interacts with a second fusion protein comprising full-length wild-type HIV1 GAGp6 fused to a DNA binding domain, but fails to interact with three other second fusion proteins comprising variants of full-length HIV1 GAGp6 with three different mutations in the late domain PTAP motif. Further, Example 4 (pages 83-84) demonstrates that a first fusion protein comprising HIV1 GAGp6 fused to a GST tag interacts with a second fusion protein comprising amino acid residues 1-207 of Tsg101 fused to a myc tag, and further demonstrates that a peptide comprising only the first 14 amino acid residues of HIV1 GAGp6 is capable of disrupting the binding of these first and second fusion proteins.

Besides these specific examples, which were actually reduced to practice by the inventors, the specification of the instant application, as previously mentioned, teaches that the UEV domain of Tsg101 and the PTAP motif of the late domain of HIV GAGp6 are responsible for the interaction between these two proteins (page 38, lines 5-6). Further, with respect to fragments of HIV GAG that retain the ability to interact with Tsg101, the specification teaches: "the first 14 amino acid residues of HIV GAGp6 (which includes the PTAP late domain motif) are sufficient in binding to the N-terminal portion of Tsg101 (amino acid residues 1-207, which includes the Tsg101 UEV domain)" (Specification, page 34, line 29 through page 35, line 2). Also, with respect to fragments of Tsg101 that retain the ability to interact with HIV GAGp6, the specification teaches

that one interacting partner in the protein complexes can be "e.g., a fragment containing the UEV domain of the Tsg101 protein, specifically the amino acid residues 1-207, the amino acid residues 1-147, etc." (Specification, page 38, lines 24-29). Furthermore, the specification also teaches:

> In addition, the present invention further encompasses a protein complex having Tsg101 interacting with a homologue, derivative or fragment of HIV GAGp6. In yet another embodiment, a protein complex is provided having a homologue, derivative or fragment of Tsg101 and a homologue, derivative or fragment of HIV GAGp6. In other words, one or more of the interacting protein members of a protein complex of the present invention may be a native protein or a homologue, derivative or fragment of a native protein.
>
> Thus, for example, one interacting partner in the protein complexes can be a complete native Tsg101, a Tsg101 homologue capable of interacting with the HIV GAGp6, a Tsg101 derivative, a derivative of the Tsg101 homologue, a Tsg101 fragment capable of interacting with HIV GAGp6 (e.g., a fragment containing the UEV domain of the Tsg101 protein, specifically the amino acid residues 1-207, the amino acid residues 1-147, etc.), a derivative of the Tsg101 fragment, or a fusion protein containing (1) complete native Tsg101, (2) a Tsg101 homologue capable of interacting with the HIV GAGp6 or (3) a Tsg101 fragment capable of interacting with HIV GAGp6.
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> (Specification, page 38, lines 15-31.)

While the specification clearly does not teach all possible workable embodiments of the claimed invention, it does teach multiple representative embodiments of the claimed invention, which, in view of the Federal Circuit's ruling in Invitrogen, is more than sufficient to meet the written description requirement of 35 U.S.C. § 112, first paragraph.

In view of the above, Applicants respectfully submit that the disclosure of the instant Application clearly satisfies the written description requirement for the pending claims under 35 U.S.C. § 112, first paragraph. Hence, the rejection should be rescinded.

Enablement

The issue of enablement of biotechnological inventions under 35 USC § 112, first paragraph, was also addressed by the Federal Circuit in Invitrogen Corporation v. Clonetech Laboratories, Inc., 429 F.3d 1052 (Fed. Cir. 2005). In Invitrogen the Federal Circuit considered whether the as-filed disclosure sufficiently enabled claims that

describe genetically engineered (modified) Reverse Transcriptase (RT), such as that defined in claim 1 of U.S. Patent No. 6,063,608 (the '608 patent), which reads

> 1. An isolated polypeptide having DNA polymerase activity and substantially reduced RNase H activity, wherein said polypeptide is encoded by a modified reverse transcriptase nucleotide sequence that encodes a modified amino acid sequence resulting in said polypeptide having substantially reduced RNase H activity, and wherein said nucleotide sequence is derived from an organism selected from the group consisting of a retrovirus, yeast, Neurospora, Drosophila, primates and rodents.

'608 patent, col. 19, lines 26-34 (claim 1), included as *Exhibit B*.

Close examination of this claim reveals that it reads upon a genus of highly variant RTs having substantially reduced RNase H activity, that are encoded by modified RT nucleotide sequences that encode modified amino acid sequences, wherein said nucleic acid sequences are derived from a collection of organisms, including organisms from the very diverse groups known as "retroviruses" and "yeast," among others. Importantly, the claim does not indicate exactly how the nucleotide sequence, and hence the amino acid sequence, is to be modified to encode the modified polypeptide. Furthermore, the claim makes no mention of any sort of reference sequence of either nucleotides or amino acids, or to specific regions of the isolated protein that are modified. Instead, the claim defines the invention with functional limitations by indicating that the isolated polypeptide is a modified RT having DNA polymerase activity and substantially reduced RNase H activity.

Notably, at the beginning of its ruling concerning the enablement of these claims to isolated polypeptides "encoded by a modified amino acid sequence," the Federal Circuit observed "[i]t is undisputed that by 1988 those skilled in the art knew several techniques for altering genetic sequences, including deletion and point mutations." Invitrogen, at 1070. This statement is relevant to the inquiry of enablement of the presently claimed invention, since Applicants have argued that fragments, homologues, and fragments of homologues of the interacting proteins Tsg101 and HIV GAGp6, could be readily created by one of ordinary skill in the art at the time the instant Application was filed, using routine experimentation.

In Invitrogen, the Federal Circuit next notes that the specifications of the patents-in-suit describe how to implement the claimed invention by deletion mutation; whereas the parties disagree as to whether they also teach how to implement the claimed invention by point mutation rather than deletion mutation.

Inspection of the '608 patent specification (see *Exhibit B*) reveals that while it discloses two different nucleotide sequences bearing deletion mutations (one in Figure 6 and from columns 5 through 8, and one from columns 2 through 6) that potentially encode two different embodiments of the claimed invention, both of these nucleotide sequences were created by making deletion mutations of the wild-type M-MLV coding sequence, and, only the first of these (the RT coding sequence of plasmid pRTdEcoRV-C that encodes the N-terminal most 504 amino acid residues of M-MLV RT) was shown to encode a polypeptide having the functional features of the claimed invention. Closer inspection of the '608 patent specification reveals that while it generally teaches that of the 684 amino acid residues in the cloned wild-type M-MLV RT, "residues between amino acid 212 and 314 are required for DNA polymerase activity, and residues between amino acid 503 and 601 are required for RNase H activity" ('608 patent, column 17, rows 45-48), it does not provide any teachings as to which individual amino acid residues of wild-type M-MLV RT are critical for enzymatic function, and how these residues are to be changed to create the claimed invention by point mutation. In other words, the '608 patent specification provides essentially no teachings on how to create an isolated RT polypeptide bearing a point mutation that would have DNA polymerase activity and substantially reduced RNase H activity. Furthermore, the '608 patent specification provides absolutely no teachings on which regions of RTs derived from organisms other than M-MLV are responsible for DNA polymerase activity and RNase H activity. Thus, the '608 patent specification provides no teachings on how to create an isolated RT polypeptide having the claimed functional features from any species other than M-MLV.

In view of these apparent deficiencies in the specification, Clonetech, the defendant, argued that the District Court erred, as a matter of law, in concluding that Invitrogen's claims are enabled. Clontech's contention rested on Invitrogen's failure to explain in the specification how to achieve RNase H minus RT using point mutations. Since the law requires the inventor to enable claims thoroughout the full scope without

requiring undue experimentation by those having ordinary skill in the art, Clonetech argued that Invitrogen's written description fails to enable claims encompassing RNase H minus RT made by the introduction of point mutations. Recognizing that the claims-in-suit do not exclude point-mutated RNase minus RT, Clonetech concluded that the claims must be invalid for lack of enablement.

In response the Federal Circuit ruled:

> "This argument mistakes the purpose of the enablement requirement. Section 112 requires that the patent specification enable "those skilled in the art to make and use the full scope of the claimed invention without 'undue experimentation'" in order to extract meaningful disclosure of the invention and, by this disclosure, advance the technical arts. Koito Mfg., 381 F.3d at 1155 (quoting Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (citation omitted)). Because such a disclosure simultaneously puts those skilled in the art on notice of the enforceable boundary of the commercial patent right, the law further makes the enabling disclosure operational as a limitation on claim validity. "The scope of the [patent] claims must be less than or equal to the scope of the enablement. The scope of enablement, in turn, is that which is disclosed in the specification **plus the scope of what would be known to one of ordinary skill in the art without undue experimentation**." Nat'l Recovery, 166 F.3d at 1196....
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> Although Clonetech's validity argument might have force had Invitrogen limited its claims to modified RT by reference to point mutation, Clonetech overlooks the fact that **the claims are not limited by the method of achieving the mutation**. As the district court noted, "**[t]he enablement requirement is met if the description enables any mode of making and using the invention**." Johns Hopkins Univ. v. Cellpro, Inc., 152 F.3d 1342, 1361 (Fed. Cir. 1998); accord Amgen Inc. v. Hoechyst Marion Roussel, Inc., 314 F.3d 1313, 1335 (Fed. Cir. 2003); Engel Indus., Inc. v. Lockformer Co., 946 F.2d 1528, 1533 (Fed. Cir. 1991). **In this case Invitrogen's teachings regarding deletion mutation is sufficient to satisfy its part of the patent bargain, as it fully teaches a mode of making the claimed invention.**
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> Clonetech mistakenly relies on our decision in National Recovery to support its nonenablement argument. In National Recovery the court affirmed judgement that a patent claim was invalid for lack of enablement. 166 F.3d at 1198. The claim was to method, not a compound. The claimed method called for selecting certain signals for processing, yet the written description failed to teach one of ordinary skill in the art how to select among various candidate signals. Id. at 1196. A person of ordinary skill, reading the patent, would have been required to engage in undue experimentation before reaching **a means** of practicing the claimed

> method. In short, the National Recovery enablement problem **concerned a failure to disclose any way to practice the claimed method. In this case, by contrast, Invitrogen fully describes an operable method for achieving the claimed mutation.**
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> **Enablement does not require the inventor to foresee every means of implementing an invention at pains of losing his patent franchise. Were it otherwise, claimed inventions would not include improved modes of practicing those inventions. Such narrow patent rights would rapidly become worthless as new modes of practicing the invention developed, and the inventor would lose the benefit of the patent bargain.**
>
> The court therefore affirms the district court's judgement that the claims at bar are not invalid for lack of an enabling disclosure on point mutation."

Invitrogen at 1070-71 (emphasis added).

Applicants respectfully assert that, although the claims at issue in Invitrogen read upon an enzyme with specific functional characteristics, whereas the rejected claims in the present case read upon an isolated protein complex comprising two interacting polypeptides, the decision of the Federal Circuit in Invitrogen has bearing on the present case. In particular, Applicants assert that the claims at issue in the present Application are enabled by the specification because the specification fully describes an operable embodiment of the claimed invention. In fact, the specification describes multiple embodiments of fragments of Tsg101 interacting with fragments of HIV GAG or GAGp6. For example, Table 1 on page 14 provides one representative embodiment of the present invention that was reduced to practice. Table 1 indicates that a 52 amino acid fragment of HIV Gag (comprising the GAGp6 late domain) interacts with amino acid residues 7 through 390 of Tsg101. Additionally, Example 3 (pages 81-83) shows that a first fusion protein comprising full-length Tsg101 fused to a transcriptional activation domain interacts with a second fusion protein comprising full-length wild-type HIV1 GAGp6 fused to a DNA binding domain, but fails to interact with three other second fusion proteins comprising variants of full-length HIV1 GAGp6 with three different mutations in the late domain PTAP motif. Further, Example 4 (pages 83-84) demonstrates that a first fusion protein comprising HIV1 GAGp6 fused to a GST tag

interacts with a second fusion protein comprising amino acid residues 1-207 of Tsg101 fused to a myc tag, and further demonstrates that a peptide comprising only the first 14 amino acid residues of HIV1 GAGp6 is capable of disrupting this interaction.

Besides these specific examples, which were actually reduced to practice by the inventors, the specification of the instant application, as previously mentioned, teaches that the UEV domain of Tsg101 and the PTAP motif of the late domain of HIV GAGp6 are responsible for the interaction between these two proteins (page 38, lines 5-6). Further, with respect to fragments of HIV GAG that retain the ability to interact with Tsg101, the specification teaches: "the first 14 amino acid residues of HIV GAGp6 (which includes the PTAP late domain motif) are sufficient in binding to the N-terminal portion of Tsg101 (amino acid residues 1-207, which includes the Tsg101 UEV domain)" (Specification, page 34, line 29 through page 35, line 2). And with respect to fragments of Tsg101 that retain the ability to interact with HIV GAGp6, the specification teaches that "one interacting partner in the protein complexes can be "e.g., a fragment containing the UEV domain of the Tsg101 protein, specifically the amino acid residues 1-207, the amino acid residues 1-147, etc." (Specification, page 38, lines 24-29).

Like the single deletion mutant described in Invitrogen's '608 patent, the interacting fragments of Tsg101 and HIV GAG described in Table 1 of the instant Application, are sufficient to satisfy the Applicant's part of the patent bargain, as they fully teach a mode of interacting first and second proteins required to make and use the isolated protein complex of claimed invention. Further, as noted, while the scope of a patent's claims must be less than or equal to the scope of the enablement, the scope of enablement, in turn, is that which is disclosed in the specification **plus the scope of what would be known to one of ordinary skill in the art without undue experimentation**. Nat'l Recovery, 166 F.3d at 1196 (Fed. Cir. 1999), emphasis added.

With respect to the concept of "undue experimentation" as regards the current invention, Applicants respectfully assert the following activities do NOT represent "undue" experimentation to an individual of ordinary skill in the art of molecular biology:

1. Using the BLAST algorithm to identify amino acid sequences of proteins at least 75% identical to human Tsg101 or HIV1 GAGp6 from the *Entrez* database of the National Center for Biotechnology Information.

2. Testing whether or not the homologous proteins so identified are capable of interacting with a partner protein in a manner analogous to the orthologs disclosed in Table 1 of the specification.

3. Aligning the amino acid sequences of the interaction-competent homologous proteins, in order to determine regions of amino acid conservation in these aligned homologues.

4. Identifying such conserved regions and using this information to direct the preparation of fragments of the homologous proteins that, more likely than not, retain the ability to interact with a partner protein in a manner analogous to the orthologs disclosed in Table 1 of the specification.

5. Preparing fragments of the homologous proteins and testing them for their ability to interact with a particular partner protein.

Applicants respectfully assert that while these activities may involve considerable experimentation, they do not represent "undue" experimentation to one of ordinary skill in the art of molecular biology, and they allow that skilled artisan to practice the claimed invention commensurate with the scope of the pending claims. Applicants further note that while these exercises would not be "undue" to one of ordinary skill in the art, they would be also not be necessary, since that skilled individual could practice a preferred embodiment of the claimed invention using the portions of the interacting human proteins specified in Table 1, or in Examples 3 or 4, of the as-filed specification.

Additionally, it is noted that both Tsg101 and HIV GAGp6 were known in the art and were well characterized at the time the instant Application was filed. It is also noted in the field of molecular biology, specifically in proteomics, the phenomenon of protein-protein interactions was well understood, and methods for detecting specific protein-protein interactions were well known and routine, at the time of filing. Thus, it would have been apparent to an ordinarily skilled person in the art of molecular biology that,

apprised of the disclosure of the instant Application, that no undue experimentation would be required to provide a nucleic acid encoding a protein having an amino acid sequence greater than 75% identical to Tsg101 which is capable of interacting with HIV GAGp6.

To elaborate, at the time the instant Application was filed, it was a routine task for a skilled artisan to identify proteins homologous or orthologous to human Tsg101 and to align such proteins and identify regions of conservation. It was also routine for a skilled artisan to determine the percentage identity of a given protein relative to human Tsg101, and to recognize whether a particular protein is at least 75% identical to human Tsg101. A skilled artisan could also easily identify regions of homologous proteins showing conservation of amino acid sequence and determine the percent identity of equivalent regions of homologous proteins. Moreover, since procedures for making variant proteins with substitutions, deletions, insertions and additions were routine in the art, in combination such skills would allow a person of ordinary skill to routinely create nucleic acids encoding polypeptides that are at least 75% identical to human Tsg101, and that, more likely than not, retain the ability to interact with HIV GAGp6.

Evidence in support of the assertion that individuals of skill in the art can readily identify naturally occurring orthologous protein pairs that retain the ability to interact can be found in the scientific literature from well before the filing date of the instant Application. Such reports provide clear evidence of the high level of skill in the relevant art of identifying naturally occurring orthologous proteins that retain the ability to interact that existed at the time the instant Application was filed.

The Final Office Action (page 4) states: "the specification, while being enabling for GAGp6 (449-500) and TSG101 (7-390), does not reasonably provide enablement for all other fragments, [homologues], portions with less than 100% identity, and other GAGs or TSGs." "The grounds for enablement clearly include the requirement to make and use the product. The [enablement] rejection is not based on how to make proteins but on what proteins/polypeptides are able to bind to form a complex as required by the claims."

Applicants respectfully assert that, as with Clontech's argument in Invitrogen, "[t]his argument mistakes the purpose of the enablement requirement. Section 112

requires that the patent specification enable "those skilled in the art to make and use the full scope of the claimed invention without 'undue experimentation'" in order to extract meaningful disclosure of the invention and, by this disclosure, advance the technical arts. Koito Mfg., 381 F.3d at 1155 (quoting Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (citation omitted)). Because such a disclosure simultaneously puts those skilled in the art on notice of the enforceable boundary of the commercial patent right, the law further makes the enabling disclosure operational as a limitation on claim validity. "The scope of the [patent] claims must be less than or equal to the scope of the enablement. The scope of enablement, in turn, is that which is disclosed in the specification **plus the scope of what would be known to one of ordinary skill in the art without undue experimentation**." Nat'l Recovery, 166 F.3d at 1196...." Invitrogen at 1070 (emphasis added).

Applicants respectfully contend that they have more than met their part of the patent bargain, because a person of ordinary skill in the art, upon reading the present Application would not have been required to engage in undue experimentation before reaching a means of practicing the claimed method, since the instant Application discloses multiple operative embodiments – three of which were actually reduced to practice – comprising three different sets of fusion proteins further comprising different fragments of Tsg101 interacting with different fragments of HIV GAG.

Furthermore, Applicants note that their claims to an isolated protein complex are not limited by the exact composition of the interacting proteins. They fully teach three different protein complexes in which different fragments of Tsg101 have been shown to interact with different fragments of HIV GAG. These operable embodiments of the claimed invention, when combined with the scope of what would be known to one of ordinary skill in the art without undue experimentation is clearly enough to meet the enablement requirement under the bar elucidated in Invitrogen.

In view of the arguments presented above, Applicants respectfully assert that the specification, as filed, provides adequate teachings on how to make and use the claimed invention, thereby meeting the enablement requirement under 35 U.S.C. § 112, first paragraph. Consequently, the rejection should be rescinded.

Breadth of the Claims and Meaningful Patent Protection

> Enablement does not require the inventor to foresee every means of implementing an invention at pains of losing his patent franchise. Were it otherwise, claimed inventions would not include improved modes of practicing those inventions. **Such narrow patent rights would rapidly become worthless as new modes of practicing the invention developed, and the inventor would lose the benefit of the patent bargain.**
>
> Invitrogen at 1071, emphasis added.

As a final matter regarding both the written description and enablement requirements of 35 USC § 112, first paragraph, the examiner has essentially argued that specification provides insufficient written description and enablement for the pending claims, because the claims are overly broad. Applicants do not deny that the claims are broad, but they take exception to the assertion that they are overly broad. Indeed, the reason the claims were written broadly in the first place was to provide protection against individuals "designing around" the claims by, for example, simply isolating naturally-occurring orthologs or paralogs of human Tsg101 that still retain the ability to interact with the late domain of HIV GAGp6, or alternatively, by engineering variants of human Tsg101 that retain the ability to interact with the late domain of HIV GAGp6.

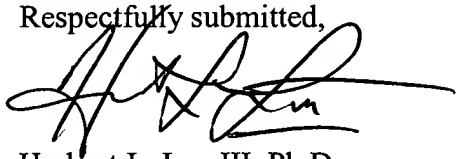
The fact that such scenarios can be readily envisioned, and were of concern to the Applicants at the time the Application was filed, supports the fact that the level of skill in the art was very high, and that there was a reasonable expectation of success of someone seeking to design around the claims by identifying naturally-occurring orthologs or paralogs, or creating synthetic homologues of human Tsg101, that retain the ability to interact with the late domain of HIV GAGp6. Indeed, because of this high level of skill in the art, only broad claims can provide meaningful exclusivity protection for the contribution made by the inventors to the art – exclusivity protection that they are entitled to under the law, upon fulfilling their part of the patent bargain – full disclosure of their invention.

CONCLUSION

In view of the recent Federal Circuit decision in Invitrogen, Applicants respectfully submit that, contrary to the allegations of the Examiner, claims 1-23, 26, 44-50 and 61-68 are indeed based upon a disclosure that provides sufficient written description and enablement, to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate with the scope of the claims. Consequently, Applicants firmly believe that the pending claims are patentable. Applicants also believe that the pending claims are presently in condition for allowance, and therefore respectfully request prompt issuance of a Notice of Allowance. Should the Examiner determine that additional issues remain which might be resolved by a telephone conference, he is invited to contact Applicants' undersigned agent.

Since this response under 37 C.F.R. § 1.116 is being provided within three months of the mailing date of the Final Office Action, is not believed that any time extension or fees are required for the filing of this response. If this is incorrect, an extension of time as deemed necessary is hereby requested, and the Commissioner is hereby authorized to charge any appropriate fees or deficiency or credit any over payment to Deposit Account no. **50-1627**.

Respectfully submitted,



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